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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,070	LEVY, GARY	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/7/3* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

On page 5 of the response, applicant cancelled claims 11, 12, 14, 15, as well as non-elected claims 1-10, 13, 16-18 and added new claims 19-32.

Upon further consideration, new grounds of rejection are established.

Election/Restrictions

A portion of newly submitted claim 19 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claim is drawn to administering an effective amount of an inhibitor of LF-A1 gene or protein. Applicant elected an antisense oligonucleotide in paper no. 7 in the elected method to inhibit an LF-A1 gene. The non-elected antibody would be required to inhibit the LF-A1 protein, see page 7, lines 13-15 of the disclosure. Since applicant did not elect the antibody, the LF-A1 protein recited in newly presented claim 19 is drawn to a non-elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the LF-A1 protein recited in claim 19 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted that newly presented claim 31 states that the inhibitor is an inhibitor of the LF-A1 gene. Since the LF-A1 protein recited in claim 19 is withdrawn from consideration, claim 31 would fail to further limit claim 19 upon cancellation of the non-elected LF-A1 protein.

Claim Objections

Claim 19 is objected to because of the following informalities: the claim recites non-elected subject matter, an LF-A1 protein. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is incomplete because there is no correlation between the method steps and the object of the method recited in the preamble. This rejection also affects claims 20-32.

Claim 22 states that the inhibitor of the LF-A1 protein is an antisense oligonucleotide sequence. It is unclear how the oligonucleotide would be able to bind and subsequently inhibit an LF-A1 protein that is composed of amino acid residues and a particular folded structure. Does applicant intend "protein" recited in line 2 of the claim to be "gene"? The claim also states that the sequence of the oligonucleotide comprises a sequence that is complementary to a "portion of the fgl-2 promoter region". The "portion" is indefinite because it is unclear which portion of the promoter region is being referred to. This rejection also affects claims 23-29.

Claim 22 recites the limitation "fgl-2 promoter region" in line 3. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant asserts that there is ample written description for the instant claims, drawn to inhibiting LF-A1 to block flg-2 induction in order to prevent or reduce immune coagulation. Applicant argues that the invention has been described with sufficient detail to convey possession of the invention and that the skilled artisan would be able to identify inhibitors and antisense oligonucleotides to use in the method.

Applicant's arguments have been fully considered, but are found unpersuasive. The inhibitor of claims 19-21 and 31 is only characterized by the function of inhibiting the LF-A1 gene. There is no structure for the claimed inhibitor and the skilled artisan would be unable to envision an unidentified molecule that is capable of inhibiting an LF-A1 gene to reduce immune coagulation. The specification generally discusses inhibitors as antibodies (see pages 7-10), antisense molecules that include antisense oligonucleotides (see pages 10-13) and other "substances" (see pages 13-14) that inhibit binding of the N-protein from a hepatitis virus. However, the specification does not describe a specific inhibitor that possesses the function required by the claims.

Dependent claims 22, 26, 29, and 32 state that the inhibitor is an antisense oligonucleotide (AON) that is complementary to the fgl-2 promoter region, a "portion" of the fgl-2 promoter, the LF-A1 binding element within the fgl-2 promoter and any sequence complementary to an LF-A1 gene. The specification describes the mouse fgl-2 gene and identifies the LF-A1 binding sequence within the promoter in Figure 2. The specification also teaches that the region within the fgl-2 promoter from -372 to -306 is the site responsive to induction of the N-protein and also identifies -332 to -325 as the LF-A1 binding element region on page 28. However, the claims encompass AON complementing any fgl-2 promoter or portion of the promoter, which is not limited to the mouse fgl-2 sequence described. Applicant has not described fgl-2 sequences from any other organism. Therefore, applicant does not convey possession of fgl-2 genes from any other animal and does not convey possession of sequences that would complement these undescribed sequences. There is also no written description for sequences complementing the fgl-2 gene sequence presented in Figure 2. There is also a lack of disclosure for the LF-A1 sequence or a sequence that would be complementary to it. Therefore, the specification does not convey possession of this sequence or any sequence complementary thereto.

Claim 23 states that the AON comprises at least 8 nucleotides that is complementary to any 8 nucleic acid sequences within the fgl-2 promoter region. Claims 24, 25, 27, 28 and 30 recite specific sequences encompasses by SEQ ID NO: 1 that the AON complements. However, for reasons discussed above, the disclosure does not convey possession of any antisense sequence for the fgl-2 promoter described in Figure 2 or a fgl-2 promoter for any other animal. The specification does not teach a single antisense oligonucleotide of any length that is

complementary to any fgl-2 sequence or SEQ ID NO: 1. Nor does the specification teach an AON of any length that meets the functional requirement of the claims to inhibit an LF-A1 gene to prevent or reduce immune coagulation. In this case, the only factor present in the claims is a functional limitation for inhibition of LF-A1. There is no identification of any particular structure the inhibitor must possess. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of LF-A1 inhibitors.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of LF-A1 inhibitors, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

There is no description of an inhibitor that possesses the required function of inhibiting the LF-A1 gene to prevent or reduce immune coagulation. There is also no structural description of an antisense oligonucleotide complementing any portion of the mouse fgl-2 promoter, a fgl-2

promoter from another organism or the LF-A1 gene. Therefore, it is determined that the specification does not convey possession of any inhibitor or antisense oligonucleotide claimed. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 22 describes the inhibitor as an antisense oligonucleotide (AON) that inhibits the LF-A1 protein. The nature of the invention is drawn to inhibiting the association between a fgl-2 promoter and an LF-A1 gene to prevent or reduce immune coagulation. The claim specifies that the sequence of the oligonucleotide comprises a sequence that is complementary to the fgl-2 promoter region or a "portion" of the fgl-2 promoter. The skilled artisan would be unable to make or use the invention claimed because even if the application conveyed possession of an antisense oligonucleotide, the AON does not possess the amino acid residues or particular structural characteristics that would enable it to inhibit an LF-A1 protein. There are no working examples demonstrating inhibition of an LF-A1 protein with an AON complementary to a fgl-2 promoter sequence. There is also no guidance provided by the inventor for inhibiting a protein with an AON. There is also no evidence in the prior art indicating that an antisense oligonucleotide can inhibit a protein. The level of the skilled artisan would be incapable of performing inhibition of a protein with an AON, much less inhibiting an LF-A1 protein with an AON that is complementary to a mouse fgl-2 promoter gene disclosed in the specification to inhibit immune coagulation.

Therefore, due to the claim recitation of inhibiting an LF-A1 protein with an inhibitor that does not share the structural features necessary to inhibit binding of an LF-A1 protein, the nature of the invention, drawn to preventing or reducing immune coagulation, the lack of art for inhibiting a protein with an AON, the lack of guidance and working examples in the disclosure demonstrating how the skilled artisan would be able to practice the invention claimed, it is determined that an undue quantity of experimentation would be required of the skilled artisan to make or use the invention.

Claims 19-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues that the skilled artisan would be able to identify and isolate oligonucleotides that are useful for the instant inventions since the LF-A1 and fgl-2 mouse and human sequences are well known in the art.

Applicant's arguments have been fully considered, but are found unpersuasive.

The claims are drawn to a method of preventing or reducing immune coagulation associated with fgl-2 expression by administering an inhibitor of LF-A1 gene.

As discussed above, the disclosure does not provide adequate written description for any LF-A1 inhibitor or any antisense oligonucleotide (AON) that binds to any portion of a fgl-2 promoter region that inhibits association between fgl-2 and LF-A1. Although the specification discloses SEQ ID NO: 1 and the mouse fgl-2 sequence in Figure 2, there is no written description for antisense sequences complimenting these sequences. The disclosure also does not convey

possession of other fgl-2 sequences from other organisms or any antisense sequences that would be complementary thereto. However, the scope of the claims encompass inhibiting LF-A1 and fgl-2 association in mice as well as any animal comprising fgl-2.

The skilled artisan would be unable to practice the invention even if the application did convey possession of the antisense oligonucleotides that specifically complement portions of SEQ ID NO: 1 recited in claims 24, 27, 28 and 30. SEQ ID NO: 1 is derived from a mouse fgl-2 promoter. The skilled artisan would be unable to inhibit immune coagulation in humans with the instant antisense oligonucleotide because the oligo would be unable to bind to the appropriate sequence within the human fgl-2 promoter. The sequences encoding the fgl-2 genes are dissimilar. Ding et al. (abstract no: 365, reference no: XP-000929678 of the IDS) teaches that the sequence similarity between fgl-2 and hfgl-2 proteins is over 70% and that these proteins are 90% identical in amino acid sequence, but only at the C-terminal end. Therefore, the specific antisense oligonucleotide sequences recited in claims 24, 27 28 and 30 would not correlate to the human sequence of fgl-2 because of the 30% difference between the residues between the mouse and human fgl-2.

Further, the skilled artisan would not be able to inhibit immune coagulation associated with fgl-2 expression by administering an AON. Lonnberg et al. (Annals of Medicine. 1996; 28: 511-522) reviews the state of the art for antisense oligonucleotides and modifications to these compounds that are used to enhance the bioactivity of the oligos. Lonnberg et al. teach that unmodified oligonucleotides are vulnerable to extra- and intracellular nucleases and have a significantly short biological half-life. Although some chemical additions to AONs increase resistance to enzymes, modified forms of the oligos exhibit decreased binding affinity and

specificity to the target sequence. Lonnberg et al. conclude that while antisense oligonucleotides are attractive chemotherapeutic agents, several significant obstacles, such as lack of stability, affinity, specificity and cellular delivery remain to be resolved. Applicant does not provide any guidance to overcome any of the obstacles discussed by Lonnberg et al. There are also no working examples demonstrating the effectiveness of the specific antisense oligonucleotides claimed for inhibiting immune coagulation associated with fgl-2.

The skilled artisan would doubt that inhibition of LF-A1 binding to fgl-2 would prevent or reduce any fgl-2 associated immune coagulation. Although fgl-2 is directly linked to MHV-3 virus-induced fulminant hepatic failure in mice, fgl-2 is a factor in various diverse disorders, such as cardiovascular disorders, diabetes, gastrointestinal diseases, fetal loss syndrome, and bacterial and viral infections, see Yuwaraj et al. (Genomics. 2001; 71: 330-338). Therefore, administering an antisense oligonucleotide to inhibit binding between LF-A1 and fgl-2 would not prevent or reduce immune coagulation associated with fgl-2 in all of the various disorders. Yuwaraj et al. teach that the function of human fgl-2 is not clearly defined and the specific factors determining fgl-2 expression in humans is not known. Yuwaraj et al. also teach that is not known whether allelic variants exists in the fgl-2 gene or if the gene represents an inherited molecular determinant in human hepatitis. There is no nexus in the art between human fgl-2 and hepatitis infection.

Even if these concerns were overcome, the skilled artisan would doubt that the instant, undescribed antisense oligonucleotide inhibitors would have the desired effect on immune coagulation associated with fgl-2 expression in murine hepatitis virus infection. The working examples in the specification teach that the induction of fgl-2 is not always present in murine

models of hepatitis virus, see pages 24-27, which discusses the inability of MHV-2 to induce transcription of fgl-2. The working examples demonstrate a lack of predictability for fgl-2 expression and its putative role in every type of murine hepatitis. Therefore, the skilled artisan would not conclude that the instant antisense oligonucleotide inhibitor would be effective in hepatitis infection because of the discrepancies observed in the murine viruses and the different functions of fgl-2 in murine hepatitis.

In conclusion, the specification does not describe the claimed inhibitors. The state of the art indicates that any antisense oligonucleotide for specific sequences of SEQ ID NO: 1 would not bind to other fgl-2 sequences. Also, there is also a lack of working examples and guidance circumventing the concerns discussed by Lonnberg et al. for delivering the antisense oligonucleotide inhibitors to provide stability and resistance to *in vivo* nucleases as well as permeablizing the cell membrane in sufficient amounts to specifically block LF-A1 and fgl-2 binding. The skilled artisan would doubt that the instant inhibitor would be effective for reducing immune coagulation associated with fgl-2 because the function of fgl-2 in humans is uncharacterized. The skilled artisan would also doubt that the invention would be effective against murine hepatitis because the working examples indicate that fgl-2 expression is not always present in murine models. For these reasons, it is determined that an undue quantity of experimentation would be required of the skilled artisan to make and/or use the invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
April 17, 2003

JAMES HOUSEL 4/21/03
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